PROPOXYPHENE

Pharmacology and Toxicology

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Opioid Receptors

Propoxyphene is a "weak" opiate analgesic

	Inhibition of stereospecific binding K_i (nM)		
^{3}H-Ligand	Naloxone	D-Ala^2-D-Leu^5-Enkephalin	Ethylketo-cyclazocine
Receptor	μ	δ	κ
Morphine	6	74	167
d-Propoxyphene HCl	492	367	>1000
d-Propoxyphene Napsylate	527	412	>1000
Codeine	600	5600	>1000
Norpropoxyphene	>1000	>1000	>1000

Lochner and Hynes 1984 as cited by Nickander 1984

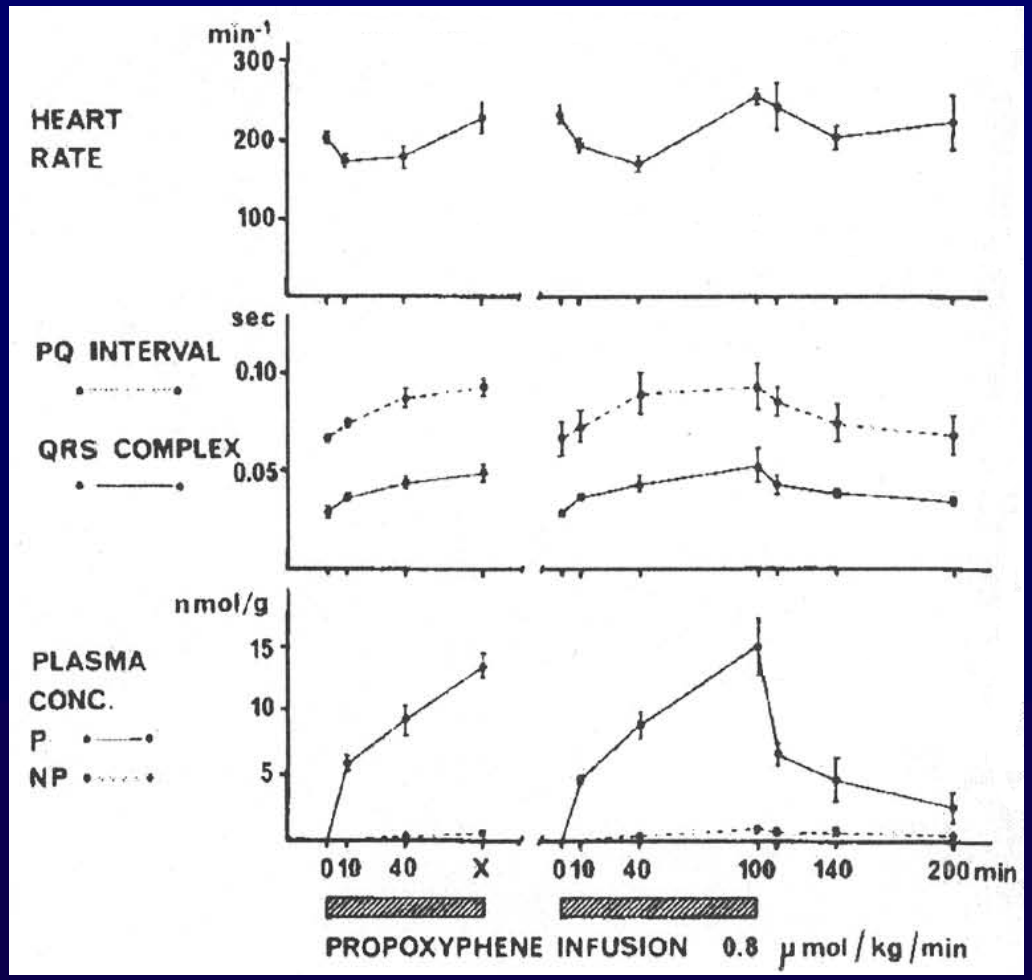
Diverse Receptor Activity

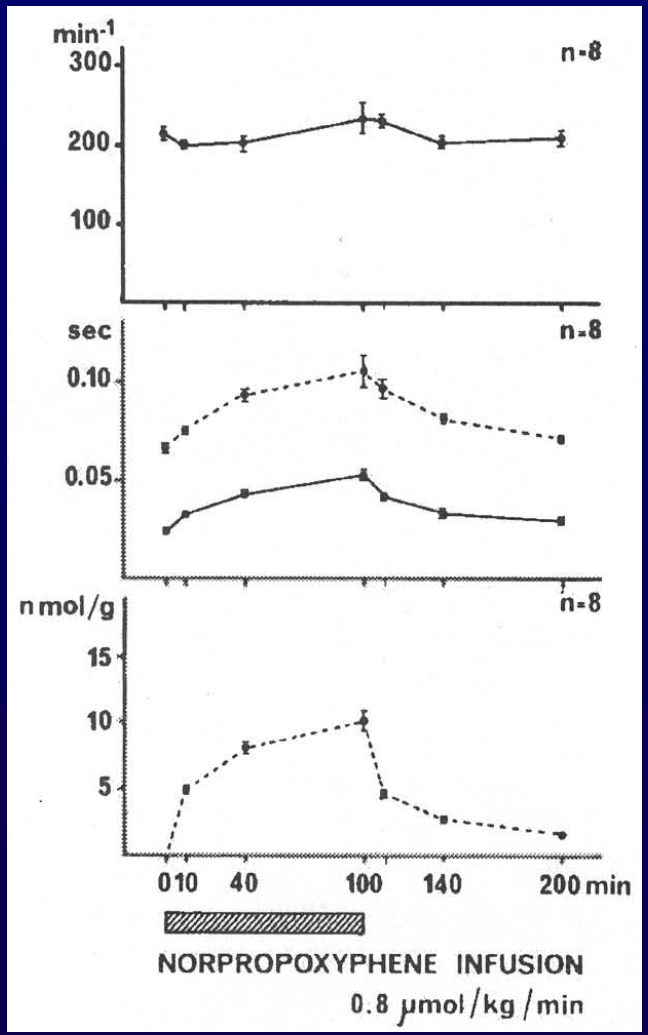
- Receptor binding studies demonstrated both propoxyphene and norpropoxyphene exhibit noncompetitive binding to:
  - **NMDA receptor** (*Ebert et al 1998a, 1998b)*
    Antagonist (IC_{50} 5 µM), **similar to methadone**
  - **Cholingeric α3β4 (neural) Nicotinic receptors**
    (*Xiao et al 2001)*
    Antagonist (IC_{50}: P 2.7 µM, NP 1.8 µM)
- Thus, both compounds have the potential for non-opioid interactions, but the significance of these findings to the overall analgesic and toxicological profile has not yet been elucidated.

Cardiac Effects

- At the 1979 AC Meeting concerns were raised about the potential abuse and toxicity of propoxyphene.
- Previously submitted nonclinical studies provided no signals suggesting heart-related concerns.
- Additional nonclinical studies were submitted that focused on cardiovascular effects.
  - Norpropoxyphene was thought to contribute to cardiac effects due to its:
    - longer half life
    - present in plasma and tissues at levels greater than propoxyphene
    - ~2-fold greater local anesthetic activity

ECG Responses In Conscious Rabbits during continuous intravenous infusion





Lund-Jacobsen 1978

ECG Responses In Conscious Dogs

Doses: Propoxyphene 0, 2.1, 6.4 or 21 µmol/kg
Norpropoxyphene 21 µmol/kg

Holland and Steinberg 1979

Parameter	Effect at an infusion dose of 21 µmol/kg	
	Propoxyphene	Norpropoxyphene
Plasma Conc at Termination	10.5 µM (3.6 µg/mL) NP was 2.5 µM	–
PR	**prolonged** ~20% (dose-related)	**prolonged, 16.6%**
QTc	**prolonged** ~10% (high dose only)	–
QRS	**prolonged** (dose-related, but large between animal variation)	–

Effects on Specific Cardiac Tissues

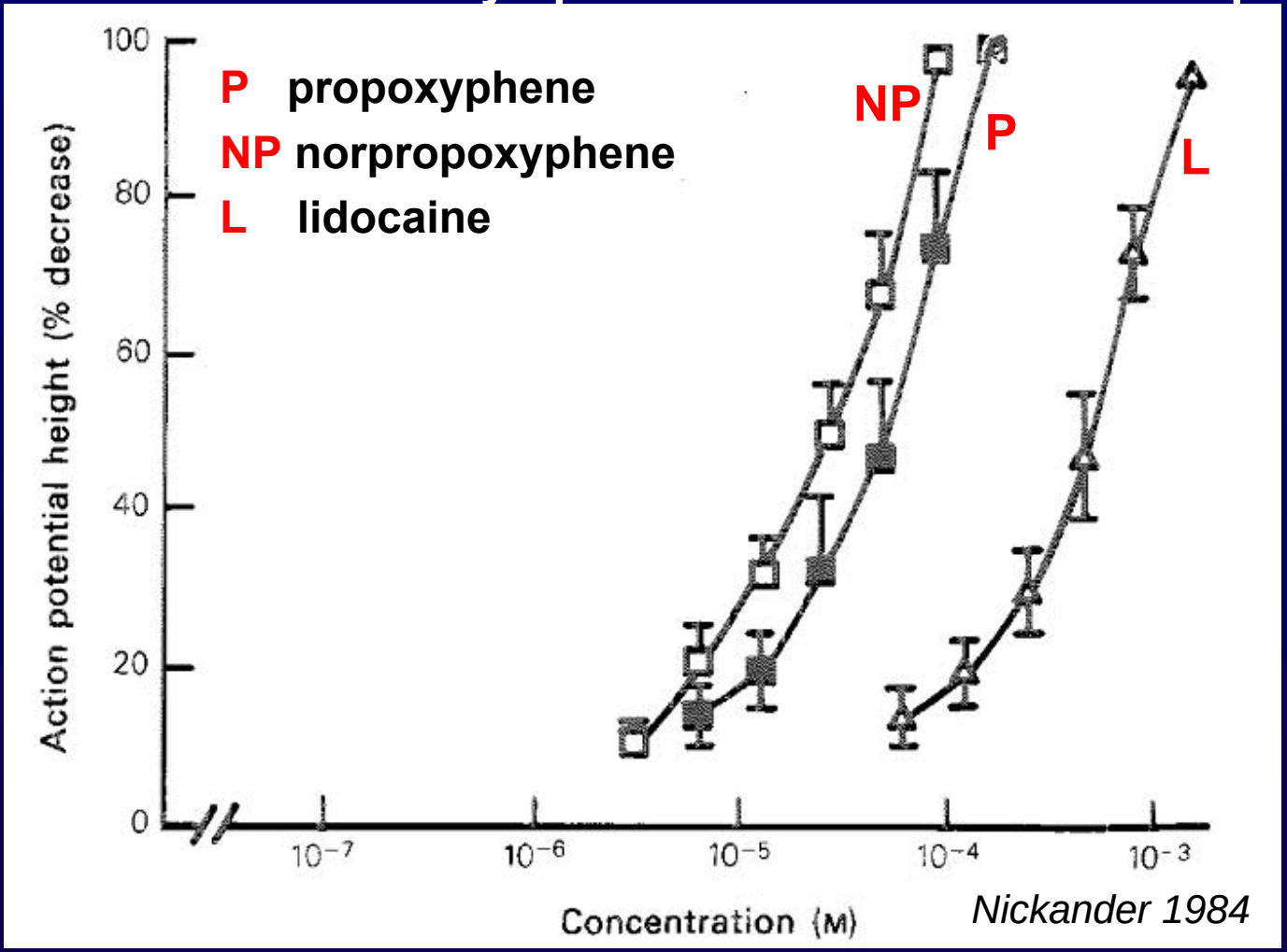
Tissue and Parameter Monitored	Effect	Potency	Tissue origin/ Study type/ Reference
Atria			guinea pig, in vitro
Sinus frequency	Slowed	P>NP	
Contractility	Reduced	NP>P	*Holland and Steinberg 1979*
His Fiber Bundle			dog, anesthetized, in vivo
H-V interval	Prolonged	NP>P	
A-H interval	Prolonged	P>NP	*Holland and Steinberg 1979*
Purkinje Fibers			dog, in vitro
Rate of rise of AP	Slowed	NP>P	
AP duration	Shortened	P=NP	
Refractory period	Unchanged	–	*Holland and Steinberg 1979*
Papillary Muscle			cat, anesthetized, in vivo
Max tension	Reduced	P>NP	*Amsterdam et al 1981*

Cardiac K^+ Channel

- Repolarization of Action Potentials in Cardiac Cells
  - involves a rapidly-activating delayed rectifier K+ current
- hERG Channel Studies of *Ulens et al (1999)*
  - Propoxyphene and Norpropoxyphene as tools to address molecular mechanisms of hERG K+ channels
  - **Both compounds altered K+ channel currents similarly**:
    - Low concentrations increased K^+ currents (ED_{50}, 5 µM)
    - Higher concentrations blocked K^+ currents ($IC_{50,}$ ~40 µM)
  - **Both compounds also altered gating currents similarly**:
    - slowed K+ channel activation
    - accelerated deactivation kinetics

Na^+ Channels

Inhibition of Cervical Sympathetic Action Potential Amplitude

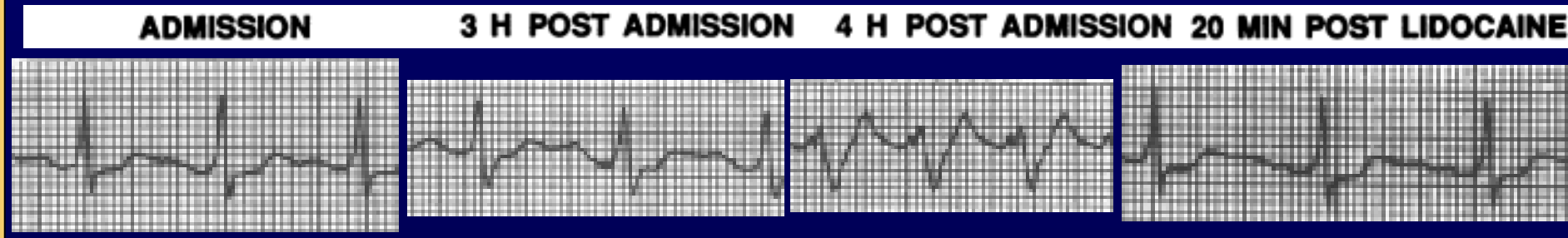


Nickander 1984

Clinical Cardiotoxicity Case Corrected with Lidocaine Therapy

Whitcomb et al 1989, case report of an overdose female patient

- Exhibited progressive QRS widening
- Reversed by lidocaine (100mg)
- Patient recovered



- Paradoxical effect since both lidocaine and propoxyphene block Na^+ channels
- Electrophysiological studies of in vitro rabbit heart atrial cells
- The faster kinetics of lidocaine was able to displace propoxyphene to facilitate the recovery of normal heart function

Summary

- Propoxyphene and Norpropoxyphene affect cardiac conduction and contractility
- Evidence exists for possible mechanisms of action
  - Na+ Channels: similar actions as local anesthetics
  - K+ Channels: blocking cardiac repolarization currents
- Evidence exists for potential activity at diverse types of receptors: Opioid, NMDA, Cholinergic Nicotinic
- The available nonclinical information is insuffiicent to enable the determination of a safety margin for therapeutic use of the propoxyphene drug products

Therapeutic Relevance

As described in the animal studies, similar cardiac-related findings (prolonged PR interval, and QRS widening) can be found in human case reports associated with drug concentrations that exceed the expected clinical therapeutic level.

However, it is unknown whether the cardiac effects noted in nonclinical studies occur in individuals exposed to therapeutic concentrations of propoxyphene drugs.